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LETTERS AND CORRESPONDENCE

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Early Ticlopidine-Induced Hepatic Dysfunction, Dermatitis and Irreversible Aplastic Anemia After Coronary Artery Stenting

To the Editor: Ticlopidine hydrochloride, a potent inhibitor of platelet aggregation, is widely used for secondary stroke prophylaxis [1]. The most common adverse effects reported with ticlopidine include diarrhea (22%), skin rash (15%), bleeding disorders (7%), hepatic dysfunction (4%), and neutropenia (2%) [1]. In 1994, 16% of the cases were fatal among 645 patients with ticlopidin-induced aplastic anemia, bone morrow suppression, and pancytopenia [2].

A 68-year-old woman was admitted to the emergency department with a three-day history of fever and skin rash. On admission, her temperature was 39°C; blood pressure, 150/80 mmHg; white blood count (WBC), 2.2 × 10^9/L (8% band, 18% monocytes, 74% lymphocytes), platelets, 95 × 10^9/L, hemoglobin (Hb) levels, 13.3 g/dL. Physical examination revealed no lymphadenopathy and hepatosplenomegaly. Liver function tests were as follows: serum aspartate aminotransferase, 423 U/L; serum alanine aminotransferase, 423 U/L, serum alanine aminotransferase, 338 U/L; gama glutamil transpeptidase, 204 U/L; alkaline phosphatase, 317 U/L; total bilirubin, 3.7 mg/dL; and direct biluribin, 2.4 mg/dL. Fourteen days before hospitalization, the patient underwent percutaneous transluminal coronary angioplasty and stenting and 500 mg ticlopidine was administered daily. At this time, complete blood count and other biochemical parameters were normal. On the eighteenth day of ticlopidine therapy, investigations disclosed a WBC of 0.4 × 10^9/L, a platelet count of 2.0 × 10^9/L, an Hb level of 9.7 g/dL with a reticulocyte count of 0.8%. Coagulation tests were normal. Diagnostic information could not be obtained by sternal bone marrow aspirate. A trephone bone marrow biopsy displayed extremely hypoplastic cellularity (5–10%) and severe aplastic anemia. In the skin biopsy, superficial perivascular dermatitis was observed. Immunoglobulin levels, autoantibodies, and hepatitis markers were normal. Repeated blood cultures wer negative. In spite of the antibiotic modifications performed to control neutropenic fever, the patient died of septic shock and multiorgan dysfunction. Postmortem percutaneous liver biopsy disclosed cholestasis.

Ticlopidine-induced severe aplastic anemia, neutropenia, and thrombocytopenia have been reported frequently. The adverse effects mentioned above are usually reversible and appear after 4–5 weeks of administration of ticlopidine [2]. Yunis et al. [3], claim that the effects of ticlopidine on bone marrow is caused by direct toxic effects other than idiosyncrasy. On the other hand, Ona et al. [4] mentioned that immunological processes could have a role in the pathogenesis. Furthermore, hepatic dysfunction was observed in patients receiving ticlopidine [1,5]. Interestingly, in our case we have observed a combination of superficial perivascular dermatitis, aplastic anemia, and hepatic dysfunction; and we have noticed that the previous ticlopidine-induced aplastic anemia cases could not have been diagnosed in a such short period of time after the therapy. Hematologic disorders caused by ticlopidine therapy may be severe and fatal. Therefore, we suggest that one should keep in mind that the patients started on ticlopidine might develop neutropenia very early in the treatment course and that complete blood counts should be monitored very closely from the beginning of therapy.

Cengiz Ceylan
Önder Kirimli
Mesut Akarsu
Bülent Ündar
Sema Güneri

Department of Internal Medicine and Cardiology, Dokuz Eylül University Hospital, İzmir, Turkey

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Low-Molecular-Weight Heparin for the Treatment of Venous Thrombosis in Patients With Adenocarcinoma

To the Editor: Venous thromboembolism is a common complication of malignancy, particularly in patients with adenocarcinoma in whom it is the second most common cause of death [1]. The treatment of these patients is difficult because conventional anticoagulation with warfarin is frequently complicated by recurrent thromboembolism [2]. Although subcutaneous unfractionated heparin (UFH) may be more effective than warfarin for the long-term management of these patients [2], UFH has a relatively short half-life necessitating frequent subcutaneous administration, has unpredict-

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able subcutaneous absorption requiring close laboratory monitoring, and is commonly associated with side effects including hypersensitivity, bleeding, and thrombocytopenia [3].

Low-molecular-weight Heparin (LMWH) has been shown to have at least equal efficacy and safety when compared with UFH for the short-term treatment of patients with venous thromboembolism [4], while having a more predictable subcutaneous absorption, longer plasma half-life and lower risk of allergic reactions, bleeding, and thrombocytopenia [3]. In addition, patients with cancer who receive LMWH for the initial treatment of venous thromboembolism have been shown to have reduced cancer-related mortality compared with those who received UFH [5], suggesting that LMWH may have a specific inhibitory effect on tumor growth that is not evident with UFH. However, the use of LMWH for the treatment of recurrent thromboembolism in patients with adenocarcinoma has not been reported previously.

We report our recent experience using LMWH for the treatment of venous thrombosis in five patients with advanced adenocarcinoma (Table I). The first three patients experienced recurrent thrombosis while taking warfarin (with international normalized ratio [INR] values in the therapeutic range), before they were successfully switched to long-term LMWH (dalteparin sodium 120 units/kg twice daily). The remaining two patients were commenced on long-term LMWH immediately after initial treatment with UFH, as they presented with extensive venous thrombosis in the setting of advanced adenocarcinoma, and were therefore considered to be at very high risk of recurrence.

All five patients remained thrombosis-free while receiving twice daily dalteparin sodium (120 units/kg). Patient two did develop recurrent venous thrombosis, but only after the dose of dalteparin sodium was reduced to a once daily prophylactic dose when he was thought to be in ''clinical remission.'' His symptoms, however, resolved when the dose of dalteparin sodium was increased to 120 units/kg twice daily, and he did not require hospitalization. Four of the five patients subsequently underwent radiotherapy and/or chemotherapy without hemorrhagic complications.

Our experience suggests that LMWH is an effective and safe alternative for the long-term management of cancer patients with venous thromboembolism, and may prove to be particularly useful in the treatment of high-risk patients with recurrent thromboembolism despite warfarin therapy. LMWH has the added advantages that it is simple to administer, is suitable for home therapy, has predictable anticoagulant activity, does not require laboratory monitoring, can minimize the frequency of hospitalization, reduces the potential for UFH-related side effects and overall has the potential to improve the quality and quantity of the remaining life of patients with terminal cancer.

Randomized treatment trials are required to confirm our observations, and may also determine the optimal dose and duration of LMWH therapy in cancer patients with venous thromboembolism. If clinical trials confirm that the use of LMWH reduces the rate of malignancy progression and confers a survival advantage, we may find that all episodes of venous thromboembolism in cancer patients are preferentially treated with these agents in the future.

JOHN W. EIKELBOOM
ROSS I. BAKER
Clinical Thrombosis Unit, Royal Perth Hospital, Perth, Australia

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TABLE I. Cancer Patients Treated With Low Molecular Weight Heparin*

Patient	Age/sex	Diagnosis (primary site)	Initial thrombosis	Treatment for initial thrombosis	Recurrent thrombosis (INR)	Treatment for recurrent thrombosis	Outcome (survival on LMW heparin)
1	39/F	Metastatic adenocarcinoma (primary unknown)	Axillary vein	UF heparin [a] and warfarin	Axillary vein (INR 3.5)	UF Heparin and LMW heparin[b]	Died of advanced malignancy (5 months)
2	68/M	Adenocarcinoma (lung)	Ilio-femoral	UF heparin[a] and warfarin	Dorsal vein of Penis (INR 4.1)	UF heparin and LMW heparin[b]	Died of advanced malignancy (7 months)
3	66/F	Adenocarcinoma (colon)	Ilio-femoral	UF heparin[a] and warfarin	Ilio-femoral (INR 3.2)	UF heparin and LMW heparin[b]	No recurrence of thromboembolism at 4 months
4	71/F	Metastatic adenocarcinoma (esophagus)	Popliteal	UF heparin[a] and LMW heparin[b]	—	—	Died of advanced malignancy (5 months)
5	58/F	Metastatic adenocarcinoma (renal)	Inferior vena cava	UF heparin[a] and LMW heparin[b]	—	—	Died of advanced malignancy (1 month)

*Dalteparin sodium. F, female; M, male; UF, unfractionated; LMW, low molecular weight; INR, international normalized ratio.
[a]UF heparin was administered intravenously for a minimum of five days.
[b]LMW heparin (dalteparin sodium) dose was 120 units/kg twice daily.

A Triple Ilematologic Nightmare: Underdiagnosing and Not Treating the Most Common US Genetic Disorder (Iron Overload): Discarding Each Year Tons of Their Good Donor Blood, Creating Artificial Donor Blood Shortages in Each of the Past 30 Years

To the Editor: In the September 1, 1997 *US News and World Report* (*USNWR*), senior writer Dana Ilawkins brought to the nation the full extent

of this problem in her story ''Throwing Out Good Blood.'' [1]. She was able to do this because of massive help lining up the facts, the doctors, and the patients who could confirm them, through three officers of the Iron Overload Diseases Association (IODA): Director of Public Relations Sandra Thomas, IODA Treasurer David Snyder (both acting for IODA President Roberta Crawford), and myself as an IODA Advisory Board member.

Mount Sinai's Blood Bank Director Morton Spivack, M.D., wrote in his September 29, 1997 letter to the editor of *USNWR* [2]: ''I have been Director of various blood banks and a member of the American Association of Blood Banks (AABB) for 34 years. In this capacity, I have lived through many blood shortages, including one just this past summer. The use of blood drawn from the many otherwise healthy patients with hemochromatosis would go a long way toward alleviating these recurrent shortages. The inability of the various regulatory agencies to see this has always amazed me. There have been arguments made that this issue is either a safety or a financial issue. Safety should not be an issue since these donors are under medical care, and in their frequent donations they are tested by a battery of tests designed to ensure the safety of their blood. As to the financial issue, this argument pales into insignificance when we consider the great addition to the US blood supply that these donors could make.''

All Americans should be blood tested (by both serum-ferritin and serum transferrin percent saturation with iron) for iron overload [3]. After these two tests confirm the diagnosis, liver biopsy is desirable to quantitate the size of liver stores and degree of liver fibrosis. High stores and fibrosis predict liver cancer if the stores are not removed. Approximately 12% of Americans (approximately 30% of African Americans) have genetic heterozygous hemochromatosis (H) (moderate iron overload) and approximately one in 100 to 200 (approximately one in 100 African Americans) have homozygous hemochromatosis (HH) (excessive iron overload) [3]. Those with H absorb approximately 50% more iron from their daily food than the rest of us, and thus need approximately four to six therapeutic phlebotomies/year to get rid of their excess body iron and maintain normal levels [3–5]. Most patients with HH are not diagnosed until organ damage (pancreas, liver, gonads, heart, joints, etc.) appears; many die undiagnosed, with autopsy revealing that their diabetes, cirrhosis, liver cancer, sterility, cardiomyopathy, arrhythmias, and/or arthritis were due to untreated iron overload. HH patients absorb daily three times the normal food iron.

When the diagnosis of H or HH is made, the patient and next-of-kin must be forcefully and directly informed that they need regular therapeutic phlebotomies and must henceforth abstain from alcohol and supplements containing iron and/or vitamin C, because any of the three will increase iron absorption and speed early organ destruction, liver cancer, and death [3–5].

FDA regulations copy those of the AABB and require that H and HH phlebotomies be stigmatized by labeling them ''therapeutic phlebotomy—patient has iron overload,'' creating an unwarranted fear resulting in healthy donor blood being thrown out rather than offered without stigma to recipients who need it, creating artificial [1,2] donor blood shortages through the US and our military overseas (including during the Gulf War, in which I served as an active-duty Green Beret Medical Officer).

On September 5, 1996, I filed a petition with the FDA to destigmatize H and HH blood [6]. On June 19, 1997, the petition was rejected on the grounds that there was not enough evidence to support it. In fact, the weekly *ABC* (American Blood Centers) *Newsletter* (November 8, 1996, p. 10) states that the FDA had recently met with the AABB, and they agreed to reject my petition on the grounds that it is not a blood bank safety issue, but a money issue (approximately $200 million/year profit from phlebotomies [1,2], therefore in the province of HCFA and not of FDA! Despite this fact, almost a year later, a Red Cross spokesman alleged (with no evidence from H or HH patients) that it was a safety issue, because H and HH individuals are ''not volunteer donors'' [7]. Blood bank director Spivack made clear [2] that this was a specious argument (see his quote in the second paragraph above).

I replied to FDA on August 14, 1997 that ''donor blood from persons with H or HH is the best donor blood for two reasons: 1. Unlike other donors, H and HH donors almost never receive transfusions, and thus almost never receive blood contaminated with AIDS or hepatitis virus; 2. Most who need blood are iron-deficient. H and HH blood is high in iron.'' I did not mention, but should have, that multiple phlebotomized hemochromatosis donors have normal to low circulating iron, and so are ideal donors for patients with anemia due to genetic hemolytic disorders (thalassemia, sickle cell disease, G6PD deficiency, etc.). Implementation of the above actions is overdue, as we noted in a recent paper [4] which focuses mainly on our new assay for ferritin iron, i.e., mean number of iron atoms per molecule of ferritin protein (the number is low in deficiency, normal in inflammation, and grossly elevated in iron overload) [5]. An FDA spokesperson telephoned me about August 28 to inform me that the FDA had received and was seriously considering my August 14 letter, but it would take some time to reach a conclusion.

Commercially available serum assay for the hemochromatosis gene [8, 9] is of less value than measuring the duo of serum ferritin protein and percent saturation of transferrin [3,5], or measuring the even better duo of serum ferritin protein and serum ferritin iron [5]. In approximately 15% of those with phenotypic iron overload disease, the currently isolated relevant genes are not found [8,9]. Also, 15% with the genotype do not express the phenotype [8,9]. Therefore, we should not, for ethical and legal reasons (i.e., losing a lawsuit to an erroneously stigmatized plaintiff), stigmatize genotypes (or adequately phlebotomized phenotypes) as having iron overload disease because about 30% do not. In early phenotypes, iron overload and its accompanying early liver fibrosis may disappear with adequate phlebotomy [10] (also see Powell [11]).

Massive further documentation of all of the facts delineated above can be found in the papers presented by many of the world's leading iron researchers, including those at blood banks all over the US and Canada, and Laurie Powell of Australia, at the CDC's second workshop on iron overload held in Atlanta, GA, March 3–5, 1997 [11]. The first such CDC workshop was on February 26 and 27, 1996, also in Atlanta. It was coordinated by Ray Yip and Sharon McDonnell. The IODA has sponsored for 15 years excellent annual Hemochromatosis Symposia. An unofficial summary of the proceedings of the 1997 workshop is available from Roberta Crawford, President, Iron Overload Diseases Association, 433 Westwind Drive, North Palm Beach, FL 33408 (Tel: 407-840-8512, 3). An excellent longitudinal review of diagnosing and treating 410 Canadians and French people with hemochromatosis appeared in Hepatology in January, 1997 [12]. Even more recently, HH was found in about 1% of German Caucasians [13]. The title of that 1998 paper echoes the title of our 1992 paper [3] in which we cited (our ref. 26 [3]) an open letter of January 20, 1992, from Dr. R. Gambino, in which he reported that a large US commercial laboratory, using measurements of serum TIBC with ferritin redux, detected iron overload in about 1% of several million patients visiting physicians' offices.

I urge *American Journal of Hematology* readers to protect their patients and themselves [14] by doing universal screening for iron overload [3,13] and to write letters in support of our petition to FDA (FDA Docket Number 96-0328/CP 1, filed September 5, 1996) [6] to destigmatize hemochromatosis blood. Write to: Dockets Management Branch, Food & Drug Administration, Department of Health and Human Services, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857. Also, Fax your letter to the FDA Dockets Management Branch at 301-594-3215.

Note: Canada ended the official stigmatization of hemochromatosis donor blood in 1991.

NOTE ADDED IN PROOF

After reviewing all the evidence, an expert panel of the CDC (Centers for Disease Control and Prevention) and the NHGRI (National Human Genome Research Institute) published in great detail [15] agreement with the position stated in the current communication, i.e., ''Genetic testing is not recommended at this time in population-based screening for hereditary hemochromatosis. . . .''

VICTOR HERBERT

Mount Sinai Hematology and Nutrition Research Laboratory, Mount Sinai and Bronx VA Medical Centers, Bronx, New York

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Androgen-Induced Erythrocytosis

To the Editor: Over 30 years ago it was reported that androgens/anabolic steroids stimulate erythropoietin (EPO) synthesis in man [1]. It has been shown that an elevated hematocrit increases risks for cardiovascular events; however, the beneficial effects of androgens in thrombocytopenia, polycythemia vera, and myelofibrosis have been demonstrated [2]. Thus, today the exact role of anabolic steroids in red cell synthesis remains unclear; however, the beneficial effects of anabolic steroids on skeletal muscle hypertrophy and strength are no longer disputed [3]. The numerous reports of myocardial infarction, stroke, and sudden death in bodybuilders using anabolic steroids typically implicate testosterone and lipoprotein alterations as the cause of death [4]. Erythrocytosis has recently been implicated as a possible side effect of long-term testosterone replacement therapy in elderly males [5]. Two of eight patients studied developed elevated hematocrits. Of interest was the development of sleep apnea in both patients duirng testosterone treatment, thus the exact cause of polycythemia was uncertain [5].

TABLE I. CBC Parameters in an Athlete on and off Anabolic Steroids*

CBC	On androgens	Off androgens	Normal range
WBC thous/mm3	6.0	5.7	4–10.5
RBC mill/mm3	6.2[a]	4.9	4.1–5.6
HGB g/dl	18[a]	14.7	12.5–17
HCT %	54.6[a]	43.5	36–50
MCV fl	84	89	80–98
MCH Pg	29	30.2	27–34
MCHC %	34.5	33.9	33.5–35.5
Neutrophils %	57	44.5	40–74
Lymphocytes %	26	36.5	14–46
Monocytes %	12.1	12.0	4–13
Eosinophils %	2	6.9	0–7
Basophils %	0	0.1	0–3
Platelet count	148	177	140–415
RDW %	14.3	12.7	11.7–15.0

*CBC, complete blood count; WBC, white blood cell; RBC, red blood cell; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.
[a]Beyond normal range.

This report involves a 28-year-old competitive bodybuilder who presented to his primary care physician (PCP) for routine examination secondary to generalized fatigue and decreased exercise endurance. The PCP initially performed a serum chemistry, blood cell count, thyroid profile, hepatitis screen and HIV test. The results were all normal except for elevations in red blood cell count, hemoglobin, and hematocrit. The PCP denied the ability of anabolic steroids to induce polycythemia and counseled the patient about polycythemia vera and myelodysplastic disease before referring him to the University of North Texas Health Science Center for further examination. Upon arrival, the patient brought three complete blood counts (CBCs) performed by his PCP which all had elevated red blood count (RBC), hemoglobin, and hematocrit. The patient denied smoking or recreational drug use but admitted to using 400 mg testosterone enanthate weekly, 100 mg testosterone propionate weekly, 40–50 mg methandrostenolone (Dianabol, oral anabolic steroid) daily. The patient had negative medical, surgical, and family histories. Initial examination included two-dimensional echocardiography which only revealed concentric left ventricular hypertrophy, with left ventricular wall thicknesses of 12 mm. There were no valvular, right-left shunts, or cardiac anomalies present. A repeat serum chemistry and CBC was also performed which revealed elevated hematocrit, RBC, and hemoglobin (Table I). EP levels were not measured. The patient was instructed to stop the anabolic steroids and to return in six weeks. The patients follow-up CBC revealed normal parameters (Table I).

While the role of androgens in hypercoagulable states is far from being understood, this case demonstrates that a common denominator in the previous reports of myocardial infarction and stroke may be a hypercoagulable state secondary to androgen-induced erythrocytosis. A review of the anabolic steroid literature has no reports of erythrocytosis in athletes using anabolic steroids. This case is the first report of erythrocytosis occurring in a healthy male bodybuilder secondary to anabolic steroid abuse.

This case further supports the suggestion of routine CBC in patients receiving testosterone-replacement therapy or athletes abusing anabolic steroids [5]. Future studies should focus on the EP levels and the incidence of erythrocytosis in athletes abusing anabolic steroids.

R.D. DICKERMAN
Department of Surgery, University of North Texas Health Science Center, Fort Worth, Texas

R. PERTUSI
N.Y. ZACHARIAH
F. SCHALLER
Department of Medicine, University of North Texas Health Science Center, Fort Worth, Texas

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